Locked Nucleic Acid (LNA™)

Custom Oligonucleotides for RNA and DNA Research

August 2009

EXIQON
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Table of contents

Locked Nucleic Acid (LNA™) technology 3
LNA™ applications overview 4
In situ hybridization and Northern blotting 5
SNP detection/Allele-specific PCR 6
Antisense inhibition 7
Custom LNA™ oligonucleotides – design 8
Custom LNA™ oligonucleotides – purification and delivery 9
Custom LNA™ oligonucleotides – labels and modifications 10
Custom LNA™ oligonucleotides – ordering information 12
Distributors 13
Contact information 14

Locked Nucleic Acid (LNA™) technology

Introduction to LNA™

Locked Nucleic Acid (LNA™) nucleosides are a class of nucleic acid analogues in which the ribose ring is "locked" by a methylene bridge connecting the 2'-O atom and the 4'-C atom (Figure 1). LNA™ nucleosides contain the common nucleobases that appear in DNA and RNA and are able to form base pairs according to standard Watson-Crick base pairing rules. However, by "locking" the molecule with the methylene bridge the LNA™ is constrained in the ideal conformation for Watson-Crick binding. When incorporated into a DNA or RNA oligonucleotide, LNA™ therefore makes the pairing with a complementary nucleotide strand more rapid and increases the stability of the resulting duplex.

The affinity-enhancing effect of incorporation of LNA™ monomers into an oligonucleotide is demonstrated by an increase in the duplex melting temperature (T_m) of 2-8 °C per LNA™ monomer (see table 1).
LNA™ oligonucleotides are defined as DNA or RNA nucleotides containing one or more LNA™ nucleosides. Since the physical properties (e.g. water solubility) of these sequences are very similar to those of RNA and DNA, conventional experimental protocols can easily be adjusted to their use.

LNA™ oligonucleotides can be synthesized by conventional phosphoamidite chemistry allowing automated synthesis of fully modified LNA™-sequences as well as chimeras with DNA, RNA, modified bases or labels.

Benefits of LNA™

- Ideal for specific detection of short RNA and DNA targets
- High affinity binding to complementary RNA results in superior potency when used for antisense inhibition
- Superior single nucleotide discrimination
- Resistant to exo- and endonucleases resulting in high stability *in vivo* and *in vitro* applications
- Increased target specificity
- Facilitates T_m normalization
- Strand invasion properties enables detection of "hard to access" samples
- Compatible with standard enzymatic processes

Figure 1

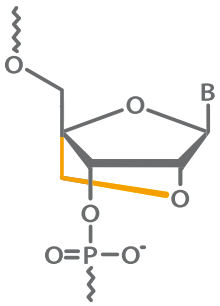


Figure 1. The structure of LNA™

Table 1

T_m increase/monomer against DNA (°C)	2-6
T_m increase/monomer against RNA (°C)	3-8
ΔT_m at single mismatch against DNA (°C)	LNA™>>DNA
Compatible with standard molecular biology	Yes
Water solubility	High

Table 1. LNA ™ properties

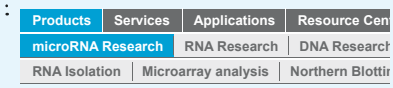
LNA™ applications overview

Studying microRNA?

Exiqon offers a range of predesigned LNA™-based products for microRNA research:

- MicroRNA isolation
- Microarray expression analysis
- Real-time PCR
- *In situ* hybridization
- Northern blotting
- Antisense inhibition

Visit exiqon.com/ls and follow the menu naviagation below to order or learn more about the miRCURY LNA™ product line.



LNA™ has been proven to be a powerful tool in many molecular biological applications in which standard DNA oligonucleotides or RNA riboprobes do not show sufficient affinity or specificity. LNA™ can be used to overcome the difficulties of studying very short sequences and has greatly improved, and in many cases enabled, specific and sensitive detection of microRNA and other small RNA molecules. Exiqon offers a range of LNA™-based products for microRNA detection, quantitation and antisense inhibition (see box to the left).

The unique ability of LNA™ oligonucleotides to discriminate between highly similar sequences has been exploited in a number of applications targeting longer RNA sequences such as mRNA. In addition, LNA™ has also been successfully used to enable detection of low abundance nucleic acids and chromosomal DNA. See below for an overview of proven LNA™ applications for the study of microRNA, other RNA molecules and DNA:

Figure 2

RNA
- *In situ* hybridization
- Northern blotting
- Antisense inhibition
- Microarray analysis
- Real-time PCR
- Isolation
- RNAi
- Gene repair/exon skipping
- Splice variant detection
- Molecular beacons

DNA
- SNP detection/Allele-specific PCR
- FISH
- Antisense inhibition
- Comparative genome hybridization

MicroRNA
- Microarray analysis
- Real-time PCR
- *In situ* hybridization
- Antisense inhibition
- Northern blotting

Other
- DNAzymes
- Zorro strand invasion
- Proteomics of isolated chromatin segments (PICh)

Figure 2. Proven LNA™ applications

On the next pages you will find a description of some of the applications listed above in the "RNA" and "DNA" categories.

Please visit exiqon.com/ls or contact us at exiqon.com/contact to learn more about LNA™-based products for microRNA research and the wide range of other LNA™ applications.

In situ hybridization and Northern blotting

RNA | *In situ* hybridization | Northern blotting

Due to their unique hybridization properties, LNA™ probes are the ideal choice for the detection of short non-coding RNAs, discrimination between different mRNA splice variants or highly similar isoforms. In addition to providing unmatched specificity, these probes give strong signals even with short hybridization periods. In some cases, LNA™ probes give over 20-times higher signal than the corresponding DNA probes and can thereby enable detection of otherwise undetectable low abundance nucleic acids (Figure 4). LNA™ probes can also be used with great advantage for sensitive Northern blot analysis and chromosomal FISH.

To learn more about LNA™ probes for *in situ* hybridization, please visit exiqon.com/ls and follow the menu navigation below or contact us at exiqon.com/contact.

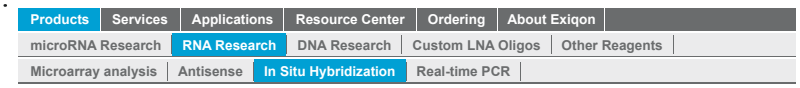


Figure 3

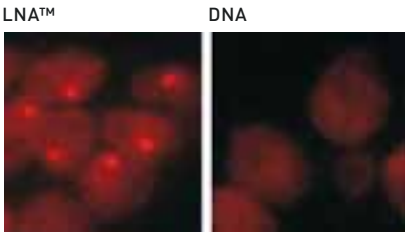


Figure 3. LNA™ enables detection of SSA4 RNA in Δrip1 fixed yeast cells. *In situ* hybridization using a single labeled Cy3™ LNA™ mRNA *in situ* hybridization probe (left figure) resulted in improved signal and less background staining compared to a single labeled Cy3™ DNA probe (right figure) of the same length. Pictures were taken after 20 min hybridization time in 50% formamide. Thomsen *et al.*, RNA. 2005; 11(11): 1745 - 1748;

Figure 4

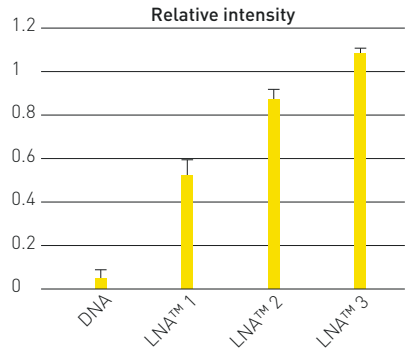


Figure 4. LNA™ *in situ* hybridization probes give stronger signals than DNA probes. The intensities of four ISH probes targeting rRNA from E. coli were compared. All probes had the same 19 nt sequence but the LNA™ probes had 1-3 LNA™ subsitutions. LNA™ 3 produced 22 times higher intensity than the DNA probe. Selected data from Kubota *et al.* Appl. Environ. Microbiol. 2006, 72: 5311-7.

SNP detection/Allele-specific PCR

DNA | SNP detection

Figure 5

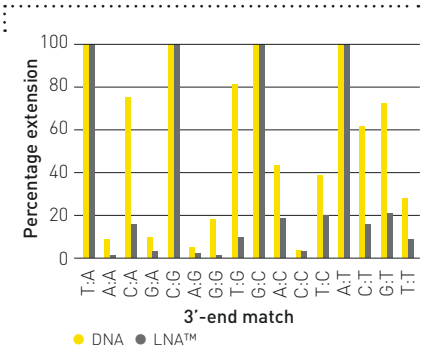


Figure 5. Superior mismatch discrimination of LNA™ primers in allele-specific PCR. Placing a 3' LNA™ residue in the primer at the SNP site improves allelic discrimination compared to an unmodified DNA primer. PCR primers with 3'-end mismatches were constructed and their ability to initiate extension was compared. DNA and LNA™ band intensities are shown as the percentage of mismatch extension from each primer variant. Latorra *et al.* Hum Mutat. 2003, 22(1): 79-85.

Figure 6

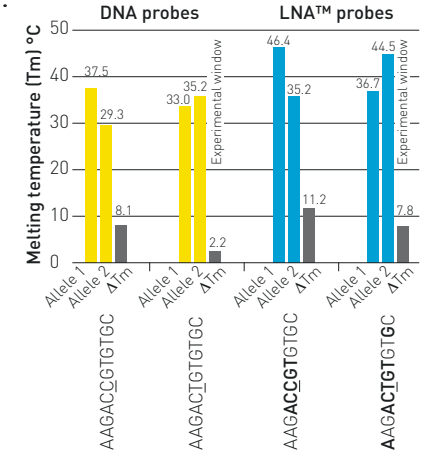


Figure 6. LNA™ probes are superior to DNA probes for SNP detection. Two capture probes targeting each of the two alleles in a SNP were enhanced by LNA™ and hybridized to the target PCR amplicon. LNA™ incorporation increases the T_m of the probes and leads to a larger ΔT_m thereby improving the the mismatch discrimination ability of the assay. Probe sequences are presented below the bars. Underlined positions indicate the site of the SNP and the nucleotides in red represent LNA™ monomers.

Single nucleotide polymorphisms (SNP) can be detected via allele-specific PCR using either SNP-specific primers or probes.

Allele-specific PCR primers have been demonstrated to be excellent tools for SNP detection. In a comparison between LNA™ primers and DNA primers, Latorra and colleagues found that LNA™ nucleosides in the 3' position of the primers dramatically improve the discriminatory power of the primer (Figure 5). Another strategy for LNA™ primer design involves incorporating the LNA™ nucleoside one position away from the 3'-end. Di Guisto and colleagues have found that such primers perform better in proof-reading allele-specific extension (PRASE) PCR experiments. (Di Giusto *et al.* Nucleic Acids Res. 2004, 32(3): e32)

A SNP detection probe needs to be able to discriminate between its target and a highly related mismatch sequence. For this discrimination to be successful, there needs to be a clear difference in the melting temperatures of the duplexes, i.e. a high ΔT_m value. The unique hybridization properties of LNA™ probes make them ideal for this application. By varying both the length of the oligonucleotide and the LNA™ content and positioning, it is possible to construct probes with comparable melting temperatures (T_m) for the alleles while keeping the difference in melting temperatures (ΔT_m) between the perfect match and mismatch binding site as high as possible. Probes as short as 12 nucleotides in length can routinely be used for SNP detection. To achieve the highest level of mismatch discrimination, the LNA™ bases should be positioned at the site of the polymorphism and, ideally, also at positions adjacent to the site.

To learn more about LNA™ oligonucleotides for SNP detection/allele-specific PCR, please visit exiqon.com/ls and follow the menu navigation below or contact us at exiqon.com/contact.

Antisense inhibition

The high affinity of LNA™ oligonucleotides to complementary nucleic acids means that LNA™:RNA duplexes are much more stable than those formed between DNA and RNA. For this reason LNA™ oligonucleotides are extremely potent antisense inhibitors, both for *in vitro* and *in vivo* use. LNA™ oligonucleotides can be transfected using standard techniques and display high nuclease resistance and low cytotoxicity. For knockdown of microRNA or other small RNAs the LNA™ antisense oligonucleotides can be designed to work by steric blocking.

Choosing to include a phosphorothioate backbone further increases nuclease resistance of the oligonucleotide and improves the efficiency of the inhibition.

To learn more about LNA™ oligonucleotides for antisense inhibition, please visit exiqon.com/ls and follow the menu navigation below or contact us at exiqon.com/contact.

LNA™ oligonucleotides can be used with great advantage in many other applications (see overview on page 3 of this folder). Learn more at exiqon.com/ls

Figure 7

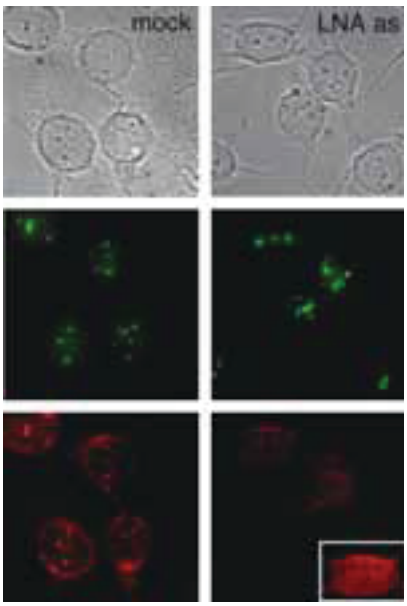


Figure 7. Effects of LNA™-mediated depletion of pRNA. Inhibition of promoter transcripts using antisense LNA™ oligos resulted in a translocation of NoRC from the nucleolus to the nucleoplasm (lower panel), while the nucleolar localization of upstream binding factor (UBF) remained unaffected (middle panel). Mayer *et al.* Mol Cell. 2006, 22: 351-361

Custom LNA™ oligonucleotides – design

Figure 8

Find useful LNA™ oligonucleotide design guidelines and design tools on exiqon.com/oligo-tools:

LNA™ Oligo Tm Prediction

Predicts the melting temperature of the LNA™ oligonucleotide.

LNA™ Oligo Optimizer

Calculates scores for self-complementarity and secondary structure of the LNA™ oligonucleotide. The scores can be used to predict the temperature at which an oligonucleotide is likely to form undesired secondary structure.

Exiqon offers synthesis of custom LNA™ oligonucleotides with a wide variety of modifications, labels, synthesis scales, purification method options, etc. (see next page).

When ordering an LNA™ oligonucleotide from Exiqon you can either design the sequence and LNA™ spiking pattern yourself or let Exiqon's experts help you with the design.

Design your own LNA™ oligonucleotide

Incorporation of LNA™ in a sequence strongly affects the properties of the oligonucleotide and great care must be taken to find the right design for your experimental purpose. While you will want to take advantage of the properties of LNA™ in order to achieve high target specificity it is important not to use too much LNA™ since this can result in a very "sticky" oligonucleotide which is hard to handle experimentally. By varying the length and LNA™ content of the oligonucleotide you need to optimize your design to achieve good mismatch discrimination, and high binding specificity, while avoiding unacceptable secondary structure and self-complementarity. Useful LNA™ oligonucleotide design guidelines and design tools are available at exiqon.com/oligo-tools (see figure 8)

Let us design your LNA™ oligonucleotide

Exiqon's in-house LNA™ experts can help you design the best LNA™ oligonucleotide for the application and target of your interest.

Your oligonucleotide will be designed for optimal LNA™ content and positioning in order to achieve optimal specificity and minimal secondary structure and self-complementarity.

To make use of this service, please provide us with the details of your request (target sequence and application) in the contact form at exiqon.com/contact.

Custom LNA™ oligonucleotides – purification and delivery

Exiqon offers custom-made LNA™, DNA and RNA oligonucleotides synthesized on a variety of synthesis scales and with a wide range of modifications (see pages 10-11) .

Purification

As standard all oligonucleotides are deprotected and desalted to remove small molecule impurities, quantitated by UV spectrophotometry to provide an accurate measure of yield and finally quality controlled (QC) by mass spectrometry.

Additional purification is recommended for many modified oligonucleotides including heavily LNA™ substituted unmodified oligonucleotides. For demanding applications, such as single nucleotide discrimination and antisense inhibition, purification may improve the performance of the oligonucleotide. In those situations we typically recommend a standard RP-HPLC purification which routinely results in >85% purity.

For long oligonucleotides (>60 bases) and for applications requiring oligonucleotides with a very high purity requirement we recommend PAGE, IE-HPLC (Ion-Exchange), or dual HPLC. RNase Free HPLC purification can be applied for oligonucleotides being used in applications sensitive to ribonucleases. Please contact us for further information regarding our purification offerings.

Na^+ Salt Exchange is available for oligonucleotides being used in applications where the presence of minute amounts of toxic salts can cause unwanted side reactions. Please view our website (exiqon.com/contact) for additional information on our analytical services.

Modifications and secondary structure of the oligonucleotide might affect yield and purity guarantees. Please contact us (exiqon.com/contact) to obtain information on guaranteed yield and purity.

Delivery

By default, oligonucleotides are delivered lyophilized in standard tubes. A number of tools for post delivery concentration adjustment are available at exiqon.com/oligo-tools (see figure 9).

Orders of 24 oligonucleotides or more can be delivered in 96-well plates. Orders of 96 oligonucleotides or more can be delivered in 384-well plates. A number of options for delivery in plates are available, e.g. normalization to the same concentration across the plate, delivery of the full yield or mixing of normalized oligonucleotides in the same well.

Please contact us (exiqon.com/contact) with any request for custom delivery of your oligonucleotides.

Figure 9

Oligo Dilution Calculator

Calculates how much water or buffer that must be added to a oligonucleotide stock solution in order to attain the desired final concentration

Oligo Resuspension Calculator

Calculates how much water or buffer is needed to resuspend a lyophilized oligonucleotide in order to attain the desired final concentration.

Oligo Concentration Converter

Calculates the concentration and total amount of oligonucleotide in your stock solution.

Custom LNA™ oligonucleotides – labels and modifications

Table 2

Mixed bases	
R = A, g	H = A, C, T
Y = C, T	B = g, T, C
M = A, C	V = g, C, A
K = g, T	D = g, A, T
S= g, C	N = A, C, g, T
W = A, T	

Table 3

Dyes

Fluoresent dyes	5'end	Internal	3' end	Excit	Emmit	Alternative
6-FAM™ (Fluorescein)	✓		✓	495	520	N/A
MAX 550	✓		✓	531	560	JOE 555 VIC 554
TYE™ 563	✓		✓	549	563	Cy3™
TEX 615	✓		✓	596	615	Texas Red®-X 617
TYE™ 665	✓			645	665	Cy5™
TYE™ 705	✓			686	705	N/A
TET™	✓			522	539	N/A
HEX™	✓			538	555	N/A
Fluorescein dT	✓	✓		495	520	N/A
Rhodamine dyes						
TAMRA™			✓	559	583	N/A
TAMRA™ NHS Ester	✓	✓	✓	559	583	N/A
ROX™ NHS Ester	✓		✓	588	608	N/A
Other						
Dy 750 NHS Ester	✓			747	776	N/A

Quenchers

	5'end	Internal	3'end
Dabcyl			✓

Phosphorylation

	5'end	Internal	3'end
Phosphorylation	✓		✓

Attachment Chemistry/Linkers

	5'end	Internal	3'end
Amino modifiers			
Amino Modifier C6	✓		✓
Amino Modifier C12	✓		
Amino Modifier C6 dT	✓	✓	
Amino Modifier			✓
Uni-Link™ Amino Modifier	✓	✓	
Labels/Antibodies			
Biotin	✓		✓
Biotin dT	✓	✓	
Biotin-TEG	✓		✓
Biotin Dual	✓		
PC Biotin	✓		

Thiol Modifiers	5'end	Internal	3'end
Thiol Modifier C3 S-S			✓
Thiol Modifier C6 S-S	✓		
Spacers and linkers			
C3	✓	✓	✓
PC Spacer	✓	✓	
Hexanediol	✓	✓	
Spacer 9	✓	✓	
Spacer 18	✓	✓	
1',2'-Dideoxyribose (dSc)	✓	✓	
I-Linker	✓		
Other			
Digoxigenin NHS Ester (DIG)	✓		✓
Cholesteryl-TEG			✓

Modified Bases

	5'end	Internal	3'end
LNA™ (Locked Nucleic Acid)	✓	✓	✓
2-Aminopurine	✓	✓	
Trimer-20	✓	✓	
Fluoro Bases	✓	✓	
2,6-Diaminopurine (2-Amino-dA)	✓	✓	
5-Bromo dU	✓	✓	
deoxyUridine	✓	✓	
Inverted dT			✓
Dideoxy-C			✓
5-Methyl dC	✓	✓	✓
deoxyInosine	✓	✓	✓
5-Nitroindole	✓	✓	
Ribo A			✓
Ribo C			✓
Ribo G			✓
Ribo U			✓
2'-O-Methyl RNA bases	✓	✓	✓

Backbone Modification

	5'end	Internal	3'end
Phosphorothioates	✓	✓	✓

Custom LNA™ oligonucleotides – ordering information

To order an LNA™ oligonucleotide from Exiqon simply

1) Design your own LNA™ oligonucleotide(s) using the design tools and guidelines on exiqon.com/oligo-tools or another design tool of your choice.
   OR
   Let Exiqon design the oligonucleotide(s) for you (contact us at exiqon.com/contact).

2) Order your oligo at exiqon.com/ls. Please find guidelines for finding the ordering web page and for typing your order below.
   OR
   Contact us exiqon.com/contact

Finding the online ordering page

Go to exiqon.com/ls and choose one of the following options:

1) Click on the highlighted custom oligonucleotide link at exiqon.com/ls

OR

2) Click on the "Custom LNA™ Oligos" menu as shown below:

Entering the oligonucleotide order

Type the sequence (5' to 3' direction)

- DNA bases: Type the base in upper case (example: A, C, T, G)
- LNA™ bases: Type the base preceded by a plus (example: +A, +C, +T, +G)
- RNA bases: Type the base preceded by an "r" (example: rA, rC, rU, rG)
- Phosphorothioated bases: Type the base followed by an "*" (example: A*, C*, T*, G*)
- 2'-O-methyl RNA bases: Type the base preceded by a lower-case "m" (example: mA, mC, mG, mU).

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Prespotted arrays
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